Hypoxia and trophoblast differentiation: a key role for PPARgamma

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Public Summary:
Tissue oxygen tension regulates differentiation of multiple types of stem cells. In the placenta, hypoxia has been associated with abnormal trophoblast differentiation and placental insufficiency syndromes of preeclampsia (PE) and intrauterine growth restriction (IUGR). Peroxisome proliferator-activated receptor-γ (PPARγ) is a ligand-activated transcription factor involved in many cellular processes, including differentiation. We have previously shown that PPARγ-null trophoblast stem (TS) cells show a defect in differentiation to labyrinthine trophoblast, instead differentiating preferentially to trophoblast giant cells (TGC). Since PPARγ is known to be regulated by hypoxia in adipose tissue, we hypothesized that there may be a link between oxygen tension, PPARγ expression, and trophoblast differentiation. We found that hypoxia reduced PPARγ expression by a mechanism independent of both hypoxia-inducible factor (HIF) and histone deacetylases (HDACs). In addition, PPARγ partially rescued hypoxia-induced inhibition of labyrinthine differentiation in wild-type TS cells but was not required for hypoxia-induced inhibition of TGC differentiation. Finally, we show that induction of labyrinthine trophoblast differentiation by HDAC inhibitor treatment is independent of both PPARγ and Gcm1. We propose a model with two pathways for labyrinthine trophoblast differentiation of TS cells, one of which is dependent on PPARγ and inhibited by hypoxia. Since hypoxia is associated with PE and IUGR, we propose that PPARγ may at least partially mediate hypoxia-induced placental insufficiency and as such may be a promising therapeutic target for these disorders.

Scientific Abstract:
Tissue oxygen tension regulates differentiation of multiple types of stem cells. In the placenta, hypoxia has been associated with abnormal trophoblast differentiation and placental insufficiency syndromes of preeclampsia (PE) and intrauterine growth restriction (IUGR). Peroxisome Proliferator-Activated Receptor-gamma (PPARgamma) is a ligand-activated transcription factor involved in many cellular processes, including differentiation. We have previously shown that PPARgamma-null trophoblast stem (TS) cells show a defect in differentiation to labyrinthine trophoblast, instead differentiating preferentially to trophoblast giant cells (TGC). Since PPARgamma is known to be regulated by hypoxia in adipose tissue, we hypothesized that there may be a link between oxygen tension, PPARgamma expression, and trophoblast differentiation. We found that hypoxia reduced PPARgamma expression by a mechanism independent of both hypoxia-inducible factor (HIF) and histone deacetylases (HDACs). In addition, PPARgamma partially rescued hypoxia-induced inhibition of labyrinthine differentiation in wild-type TS cells but was not required for hypoxia-induced inhibition of TGC differentiation. Finally, we show that induction of labyrinthine trophoblast differentiation by HDAC inhibitor treatment is independent of both PPARgamma and Gcm1. We propose a model with two pathways for labyrinthine trophoblast differentiation of TS cells, one of which is dependent on PPARgamma and inhibited by hypoxia. Since hypoxia is associated with PE and IUGR, we propose that PPARgamma may at least partially mediate hypoxia-induced placental insufficiency and as such may be a promising therapeutic target for these disorders.